REMARKS

Claims 1-14 and 43-59 were pending in the instant application. A Preliminary Amendment was filed *via* facsimile on May 22, 2002, by which new claims 44-59 were added to the application. Claims 15-42 have been cancelled, *without prejudice*, in an earlier amendment. Claims 1, 44, 52 and 53 have been amended and new claims 60-66 have been added. Therefore, claims 1-14 and 43-66 are pending in the application.

Support for the amendments to the claims as well as new claims 60-66 can be found throughout the specification and claims as originally filed. In particular, support for new claim 60 can be found in originally filed claims 1 and 12. Support for new claims 61-63 can be found at page 67, lines 36-48 of the specification. Support for new claims 64-66 can be found at page 2, lines 18-31; at page 3, lines 5-6 and at page 4, lines 13-15 of the specification.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or in one or more separate applications.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 1-14 and 43 stand rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a mutant IL8 receptor and a mutant galanin receptor, does not reasonably provide enablement for any other mutant mammalian G protein coupled receptor." The Office Action, at page 3, indicates that "[t]here is not adequate guidance as to the nature of the mutant mammalian G protein coupled receptor which Applicants claim." The Office Action further indicates that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim."

In addition, the Examiner cites multiple references to support the notion that there is unpredictability in the protein art. In particular, the Examiner cites the Gether reference for teaching that "the GPCR superfamily is large and diverse and that residues necessary for

function are not shared between families, and even within families, residues critical for function are not known." Applicants respectfully traverse this rejection.

It is Applicants' position that claims 1-14 and 43 satisfy the *Wands* factors and respectfully submit that it would be routine for one of ordinary skill in the art to generate a mutant GPCR containing a mutation in the $X_1X_2X_3X_4$ motif, which causes increased signaling as compared to the wild-type GPCR. Applicants have provided working examples that disclose how to make and express GPCRs of the instant invention, and have specifically shown that the mutant GPCRs do in fact generate a greater signal than that generated by the wild-type receptor.

With regard to the Gether reference cited by the Examiner, Applicants respectfully submit that the Gether teaches that ***"[s]ignificant sequence homology is found, however, within several subfamilies"*** (page 91). In fact, all GPCRs have similarity in their three-dimensional structures and thus act similarly in their signaling properties. Since the use of the motif of the instant invention has been shown to cause increased signaling in several GPCRs, this should be effective in all GPCRs. Thus, the broader scope claimed herein is justified.

Further, Gether indicates that there are three major subfamilies: receptors related to the "light receptor" rhodopsin and the β2-adrenergic receptor (family A); the receptors related to the glucagons receptor (family B); and the receptors related to the metabotropic neurotransmitter receptors (family C) (Gether, 2000, pg. 91). The instant invention teaches of members of the family of chemotactic cytokines, which have been proposed to be named "chemokines" for short, are being identified as vital initiators and promulgators of inflammatory and immunological reactions (Oppenheim *et al.* (1991) *Annu Rev Immunol* 9:617). Indeed the chemokines of the present invention are categorized, according to Gether, in the subfamily A, also known as the Rhodopsin/β2 adrenergic receptor-like (see Gether, 2000, page 91-92). Some of the chemokines have been assigned to a "chemokine α" subset based on their gene cluster on chromosome 4 (q12-21) and based on the fact that the first two of their four cysteine groups are separated by one amino acid (C-X-C) (see Table 1). Specifically, the application teaches that the chemokine α group includes IL-8, melanoma growth-stimulating activity (MGSA/GRO), platelet factor 4 (PF-4), β thromboglobulin (βTG), IP-10, and ENA-78 (see page 3, lines 5-6 of the specification). In addition, the specification teaches that IL-8 receptors are members of the rhodopsin receptor family and have a seven transmembrane spanning region (Holmes *et al.*(1991) *Science* 253:1278; Murphy *et al.*(1991) *Science* 253:1280) (see page 4, lines 13-15 of

the specification). Thus, Applicants respectfully submit that while GPCRs may comprise the largest superfamily of proteins, there is significant sequence homology within the subfamilies.

Independent claims 44, 52 and 53, and the claims depending therefrom, are clearly fully enabled. The Examiner admitted this at page 2 of the last Office Action, which states ***that the specification is "enabling for a mutant IL8 receptor and a mutant galanin receptor."***

In addition, Applicants submit that new claim 60, which specifically recites the specific group of wild type G protein coupled-receptors, including human galanin-1 receptor, somatostatin receptor type I, somatostatin receptor type II, somatostatin receptor type III, interleukin8 (IL8) and human nociceptin receptor, is fully enabled. Applicants have specifically taught the use of each of these receptors and it would be routine for one of ordinary skill in the art to generate a mutant GPCR containing a mutation in the $X_1X_2X_3X_4$ motif, which causes increased signaling as compared to these wild-type GPCRs. Moreover, new claims 64-66 are narrowly directed to subfamilies of GPCRs and are specifically taught in the instant specification (see page 2, lines 18-31; at page 3, lines 5-6 and at page 4, lines 13-15 of the specification).

Thus, Applicants further submit that these teachings do in fact enable one of ordinary skill in the art to make and use the invention as claimed without undue experimentation. Although these teachings are directed in large part to mutations in a specific receptor the results in increased signaling, Applicants assert that these teachings constitute a blue print that enables the skilled artisan to practice the invention across a wide range of mutant GPCRs containing a mutation in the $X_1X_2X_3X_4$ motif without undue experimentation. Example 3, for example, details the generation of a mutant galanin receptor-1 (GalR1) based upon a mutation that was shown to increase IL-8A receptor signaling (page 67, lines 10-48 of the specification). The mutation that increased the IL-8A receptor response to ligand similarly caused an increased response to ligand in the Ga1R1 as well. In short, the working examples of the present invention demonstrate a correlation between the function of GPCRs, *i.e.*, enhanced signaling, and specific amino acids within the $X_1X_2X_3X_4$ motif. Applicants have clearly identified this motif, provided the location of this motif in the protein, and also provided the candidate amino acids for this motif. In addition, Applicants have actually demonstrated increased signaling by the mutant receptor as compared to the wild-type receptor.

Based on the teachings of the specification as enumerated and cited above, and still further based on the specification's working examples, ***which the Examiner clearly admits enable practice of the claimed method with the disclosed species***, Applicants submit that one

skilled in the art would be able to make and use the claimed methods without undue experimentation.

Based on the foregoing, Applicants respectfully request that the section 112, first paragraph rejection be withdrawn.

Rejection of Claims 1-14, and 43-59 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected Claims 1-14 and 43-59 under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was field, had possession of the claimed invention."

Applicants respectfully traverse the aforementioned rejection and respectfully submit that there is sufficient written description in Applicants' specification regarding the claimed molecules, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. §2163.02). "Written description may be satisfied through disclosure of relevant identifying characteristics, *i.e.*, structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, First Paragraph Written Description Requirement.* Moreover, "[a] specification may, within the meaning of 35 U.S.C., §112, First Paragraph, contain a written description of a broadly written claimed invention without describing all species that claim encompasses." *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). Moreover, the *In re Grimme* case sets out the following language with respect to the written description requirement, "[i]t may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'" *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960).

Applicants respectfully submit that the claimed genus of the mutant GPCRs of the present invention is defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. In particular, the structure of the claimed genus, *i.e.*, the *structure* of the mutant GPCR, the corresponding the *amino acid motif*

$[X_1X_2X_3X_4]$ and the *position of the point mutation* within the amino acid motifs (see page 7, line 17 through page 8, line 40 of the specification) is specifically taught in the specification. Furthermore, the instant specification teaches distinguishing structural features within the claimed genus, including putative membrane spanning domains. For example, the instant specification discloses the amino acid sequence of the rabbit IL8A receptor showing putative membrane spanning domains, *e.g.*, Arg73 (1st intracellular loop), Met246 (3rd intracellular loop) and Gly320 (C-terminal tail) (see page 10, lines 19-21 of the specification. Moreover, G protein coupled-receptors are known molecules with a conserved structure.

In summary, Applicants have described a genus of mutant GPCRs based on structural features that are common to a substantial portion of the genus and have provided within the instant specification the amino acid motifs and the point mutations within the amino acid motif that possess these features. Accordingly, Applicants submit that the present invention satisfies the requirements of 35 U.S.C. §112, first paragraph.

Rejection of Claims 1, 8, and 13 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected Claims 1-14 and 43-59 under 35 U.S.C. §112, second paragraph because "the term 'proximal' is a relative term which render the claim indefinite." Applicants respectfully traverse the foregoing rejection. However, in the interest of expediting prosecution, and in no way conceding to the validity of the Examiner's rejections, Applicants have removed the term "proximal" from the claims and inserted the phrase "closer to the C-terminal end than the N-terminal end." Applicants respectfully submit that based on the plain meaning of the amended term, in combination with the specific examples given in the specification, one of ordinary skill in the art would know that the amended term in the context of the pending claims indicates the position of the amino acid motif relative to the N-terminal and C-terminal ends; *i.e.*, the amino acid motif is closer to the C-terminus than it is to the N-terminus. Moreover, new claims 61-63 are narrowly directed to mutant mammalian G protein-coupled receptors wherein the amino acid motif commences 5-10 amino acid residues from the carboxy terminal end of the wild type amino acid sequence (see page 67, lines 36-48 of the specification).

Thus, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claim 53 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 53 as vague and indefinite in that it is drawn to an amino acid motif. According to the Examiner, it appears to be meant to be drawn to a mutant galanin receptor of claim 52 comprising the mutant amino acid motif. Applicants have amended claim 52 to be directed to a mutant galanin receptor rendering the foregoing rejection moot. Accordingly, Applicants respectfully request withdrawal and reconsideration of the following rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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